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10/729,441	12/08/2003	Rajeeva Singh	A8689	3309

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EXAMINER	
DUFFY, BRADLEY	
ART UNIT	PAPER NUMBER
1643	
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06/13/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,441	SINGH ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,6-22 and 24-37* is/are pending in the application.

4a) Of the above claim(s) *20-25,28,29 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-19,22,24,26,27,30-34 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 18, 2008, has been entered.

1. The amendment filed March 18, 2008, is acknowledged and has been entered. Claims 1, 8 and 16 have been amended.

2. The combined executed declaration under 37 C.F.R. § 1.132 by Rajeeva Singh and Nancy E. Dagdigian filed August 24, 2007, and September 28, 2007, is acknowledged and has been entered.

3. The deposit statement filed on March 18, 2008, for the Murine Hybridoma cell line EM164 which was deposited under the terms of the Budapest Treaty at the American Type Culture Collection, P.O. Box 1549, Manassas, VA 20108 under ATCC Deposit No. PTA-4457 on June 14, 2002, is acknowledged and has been entered. This statement is sufficient to establish that the deposit requirements set forth in 37 CFR 1.801-1.809 have been met for the Murine Hybridoma cell line EM164 which was deposited under the terms of the Budapest Treaty at the American Type Culture Collection, P.O. Box 1549, Manassas, VA 20108 under ATCC Deposit No. PTA-4457 on June 14, 2002.

4. Claims 1-3, 6-22 and 24-37 are pending in the application.

5. Claims 20, 21, 25, 28, 29, 35 and 36 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

6. Claims 1-3, 6-19, 22, 24, 26, 27, 30-34 and 37 are under examination.

7. The following Office action contains NEW GROUNDS of rejection.

Priority

8. With regard to the issue of priority at page 11 of the response filed Applicant has disagreed with the Examiner's position that claims 1-3, 6-19, 22, 24-27, 30-34 and 37 do not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, submitting that the instant claims are adequately enabled and have adequate written description.

In response, after careful and complete consideration, this argument is not found persuasive because claims 1-3, 6-19, 22, 24-27, 30-34 and 37 remain rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure for the reasons set forth below.

Furthermore, Applicant appears to be arguing that claims 2, 17, 30, and 32-34 benefit by the earlier filing date of the priority application because "the present application discloses the claimed agents by virtue of their incorporation by reference".

In response, this argument is not found persuasive because the issue with respect to claims 2, 17, 30, and 32-34 is that these second agents are not disclosed in the *priority* document. Although this document describes a composition comprising an antibody and a second agent, it does not describe such a composition comprising any of the agents of claim 2, nor does it describe such a composition in a kit, *per se*.

Accordingly, the effective filing date of claims 1-3, 6-19, 22, 24-27, 30-34 and 37 is deemed the filing date of the instant application, namely December 8, 2003.

Grounds of Objection and Rejection Withdrawn

9. Unless specifically reiterated below, Applicant's amendment and/or arguments filed March 18, 2008, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed September 18, 2007.

Response to the Declaration under 37 C.F.R. § 1.132

10. The combined executed declaration[1] under 37 C.F.R. § 1.132 by Rajeeva Singh and Nancy E. Dagdigian filed August 24, 2007 and September 28, 200 is sufficient to overcome the rejection of claims 1-3, 5-19, 22, 24, 26, 27, 30, 31 and 37 under 35 U.S.C. 102(a) as being anticipated by Maloney et al (Cancer Research 63:5073-5083, August 15, 2003).

As set forth in the previous office action, if an executed copy of the declaration were submitted, the declaration would be sufficient to establish that the Maloney et al. reference is not available as prior art under 35 U.S.C. § 102(a) because the declaration establishes that the other co-authors listed on this paper were not co-inventors of the subject matter disclosed.

Grounds of Objection Maintained

Specification

11. The objection to the amendment filed April 16, 2007 under 35 U.S.C. 132(a) because it introduces new matter into the disclosure, is maintained. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as

[1] Inventor Dagdigian executed a declaration filed 8/24/2007 and Inventor Singh executed a declaration with identical wording filed 9/28/2008. Accordingly, since the same declaration was executed by these inventors it is being properly considered.

follows: the paragraphs added after paragraph 92 from the DeVita et al reference that occur on pages 2-9 of the amendment.

In the response filed March 18, 2008, Applicant has traversed this objection and incorporated the argument set forth in section VII at page 19 as it pertains to the rejection of the claims as containing NEW MATTER.

In response, as further explained and incorporated herein as set forth in the below rejection of the claims as containing NEW MATTER, because Applicant did not point with any *particularity* to the disclosures in DeVita that recite these agents in the specification as *originally filed* and because at page 69, the specification discloses that, "Certain patents and printed publications have been referred to in the present disclosure, the teachings of which are hereby each incorporated in their *respective entireties*[2] by reference" amending the specification to include sections of DeVita that were not specifically identified in the specification as *originally filed*, while excluding other sections is deemed to introduce new matter into the disclosure of the invention.

Applicant is required to provide appropriate rebuttal or cancel the new matter in the reply to this Office Action.

Claims

12. The objection to claims 22, 30, 31 and 34, as being drawn in the alternative to the non-elected invention of Group III, is maintained. Applicant has requested rejoinder of the non-elected claims of Group III, upon allowance of product claims in the response to the restriction requirement filed September 9, 2006.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to

[2] Emphasis added

which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. The rejection of Claims 1-3, 6-19, 22, 24, 26, 27, 30-34 and 37 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

At page 15 of the amendment filed March 18, 2008, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but are not found persuasive for the following reasons:

Again, the considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

As currently presented, the claims are directed to a structurally and functionally diverse genus of compositions and methods of using said compositions, wherein the compositions comprise an antibody or an epitope-binding fragment thereof, wherein said antibody of said fragment specifically binds to insulin-like growth factor-I receptor, and wherein said antibody ***has the same binding specificity as murine antibody EM164***, and wherein said antibody or said fragment ***is substantially devoid of agonist activity***; and a therapeutic agent. Claim 7 limits the antibody to an antibody that comprises a heavy chain variable region and a light chain variable region wherein the heavy chain variable region comprises the complementary determining regions comprising the amino acid sequences of SEQ ID NO:1-3. Claim 8 limits the antibody to

an antibody that comprises at least one heavy chain variable ***region*** and at least one light chain variable ***region*** wherein the heavy chain variable region comprises the complementary determining regions comprising the amino acid sequences of SEQ ID NO:1-3 and wherein the light chain variable region comprises the complementary determining regions comprising the amino acid sequences of SEQ ID NO:4-6. Claims 9-11 limit the antibodies to an antibody comprising a heavy chain variable region that has 90%, 95% or 100% sequence identity to SEQ ID NO:7. Claims 12-14 limit the antibodies to an antibody comprising a light chain variable region that has 90%, 95% or 100% sequence identity to SEQ ID NO:8. Claim 15 limits the antibodies to an antibody comprising a light chain variable region selected from: SEQ ID NO;9, SEQ ID NO:10, SEQ ID NO:11 or SEQ ID NO:12. Claim 16 limits the antibodies to an antibody comprising a heavy chain variable region comprising SEQ ID NO:13.

In the response filed March 18, 2008 Applicant appears to be arguing that the instant claims have adequate written description because the claims are directed to a genus of antibodies which bind a well-characterized antigen, i.e., IGF-IR (see e.g., page 18 of the response) and that the Examiner did not duly consider the scope of the claims. i.e., IGF-IR binding antibodies, in the previous Office action.

In response, as a first point, the Examiner did carefully and fully consider the scope of the claims in the previous office action. Notably, as set forth in the previous Office action the scope of the claims was an "antibody or an epitope-binding fragment thereof, wherein said antibody of said fragment *specifically binds to insulin-like growth factor-I receptor*, and wherein said antibody *has the same binding specificity as murine antibody EM164"*.

Furthermore, as set forth above, claim 1 now further recites that "said antibody or said fragment *is substantially devoid of agonist activity".* Accordingly, it is apparent that the claims are not directed to a genus of antibodies which specifically bind IGF-IR, but to many different subgenera of this genus, such as antibodies which specifically bind IGF-IR, wherein said antibody *has the same binding specificity as murine antibody*

EM164 and wherein said antibody *is substantially devoid of agonist activity* or such antibodies that comprise less than a structurally defined heavy chain variable domain comprising the 3 structurally defined heavy chain CDRs of the EM164 antibody *and* a structurally defined light chain variable domain comprising the 3 structurally defined light chain CDRs of the EM164 antibody. As will be explained in more detail below, it is these subgenera that are deemed to not have adequate written support in the instant specification.

As an initial point, Applicant is reminded that it cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Furthermore, while the Examiner agrees that the Federal Circuit has recently decided that the description of a fully characterized molecular target of an antibody is sufficient to adequately describe a genus of antibodies that binds that target (See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004)) the same court decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)).

Following the example set by the Federal Circuit in deciding *Noelle v. Lederman*, then, were the claims directed to an antibody that binds a well-characterized antigen, the written description would be met. However, as explained above, the claims are directed to many different subgenera of this genus.

Notably, as set forth in the previous Office action, while antibodies having the same binding specificity as murine antibody EM164 are not expressly defined in the specification, they are being interpreted in light of the disclosure of original claim 1, which recites that such antibodies include functional equivalents and variants of the murine antibody EM164 with mutations, deletions or insertions. Furthermore the specification discloses at page 17 that:

> "The primary amino acid and DNA sequences of antibody EM164 light and heavy chains, and of humanized versions, are disclosed herein. However, the scope of the present invention is not limited to antibodies and fragments comprising these sequences" and
>
> "The CDRs of antibody EM 164 are identified by modeling and their molecular structures have been predicted. Again, while the CDRs are important for epitope recognition, they are not essential to the antibodies and fragments of the invention".

Thus, it is apparent that the claims do not require that an antibody having the same binding specificity as murine antibody EM164 comprise any particularly identifying structural feature of the EM164 antibody nor does the specification identify these functional equivalents or variants as comprising any particularly identifying structural feature of the EM164 antibody, and for this reason, one of skill in the art would not be able to immediately envision, recognize or predict which of the antibodies that specifically bind IGF-IR *have the same binding specificity as murine antibody EM164*, or similarly which antibodies which specifically bind IGF-IR are *substantially devoid of agonist activity.*

To elaborate on this point, Mariuzza et al. (*Annu. Rev. Biophys. Biophys. Chem.* 1987; **16**: 139-159) reviews the structural basis of antigen-antibody recognition and teaches that an antibody, such as the murine antibody EM164, comprises two polypeptides, the so-called light and heavy chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six "complementarity-determining regions" (CDRs), three each from the light chain variable domain and the heavy chain variable domain. The amino acid sequences of the CDRs are hypervariable, as the amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant "framework" regions.

In view of Mariuzza et al., it is apparent that one of skill in the art could not immediately envision, recognize or identify antibodies that specifically bind IGF-IR *having the same binding specificity as murine antibody EM164* unless the antibody comprised ***a light chain variable domain and a heavy chain variable domain having***

each of the CDRs of murine antibody EM164 in their proper context of "framework" regions.

Notably, while the specification does teach that the murine antibody EM164 comprises a heavy chain variable domain comprising a CDR1 consisting of SEQ ID NO:1, a CDR2 consisting of SEQ ID NO:2, a CDR3 consisting of SEQ ID NO:3 and a light chain variable domain comprising a CDR1 consisting of SEQ ID NO:4, a CDR2 consisting of SEQ ID NO:5, a CDR3 consisting of SEQ ID NO:6, the claims are not limited to antibodies comprising a light chain variable domain and a heavy chain variable domains comprising these CDRs in the proper context of variable domain frameworks. Thus, for example, claim 8 is included in this rejection because it recites a heavy chain variable *region* comprising the complementary determining regions comprising the amino acid sequences of SEQ ID NO:1-3 and a the light chain variable *region* comprising the complementary determining regions comprising the amino acid sequences of SEQ ID NO:4-6 because one of skill in the art would not be able to immediately envision or recognize which other functional equivalents or variants containing these CDRs in a structurally undefined heavy chain variable *region* and a structurally undefined light chain variable *region* would specifically bind IGF-IR and *have the same binding specificity as murine antibody EM164* and be *substantially devoid of agonist activity*.

By way of further explanation, for example, Gussow et al. (Methods in Enzymology. 1991; 203: 99-121) teach the general methodology for making humanized antibodies; see entire document. One means for producing a humanized antibody involves grafting the six CDRs from the light and heavy chain variable domains from a murine antibody into the framework of a human antibody. However, in general, if only one or two of the CDRs from either the light or heavy chain variable domain were to be grafted, but not all three, the resultant antibody would not be expected to retain the binding affinity and specificity of the parent antibody. Therefore, since it is expected that all 6 CDRs need to be grafted into antibody framework regions to retain the requisite affinity and specificity of the parent antibody, antibody variants comprising less

than all 6 CDRs grafted into their proper context of framework regions, i.e., are not antibodies or antigen-binding fragments thereof that contain all 6 CDRs of the parent antibody, would not be immediately envisioned or recognized by one of skill in the art as having the affinity and specificity of the parent antibody.

Furthermore, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*Proc. Natl. Acad. Sci. USA*. 1987 May; **84** (9): 2926-2930) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). Chien et al. (*Proc. Natl. Acad. Sci. USA*. 1989 Jul; **86** (14): 5532-5536) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions as a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*Mol. Immunol.* 2003 May; **39** (15): 941-952) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

Despite such evident unpredictability, and the fact that certain amino acid residues within the framework regions, as opposed to the CDRs, may have importance in determining the specificity and/or affinity of an antibody for an antigen, there is near consensus in the art that the specificity of the antibody is most dependent upon the identities of the CDRs. Vajdos et al. (*J. Mol. Biol.* 2002 Jul 5; **320** (2): 415-428), for

example, states that antigen binding is primarily mediated by the CDRs more highly conserved framework segments, which connect the CDRs, are mainly involved in supporting the CDR loop conformations, and in *some cases* framework residues also contact antigen; see entire document (e.g., page 416, column 1).

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Additionally, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Although the skilled artisan could potentially screen candidate antibodies to identify those that *have the same binding specificity as murine antibody EM164* and wherein said antibody *is substantially devoid of agonist*, and comprise the requisite structural feature(s) set forth in the claims, for example, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

"Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for

patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims are directed to structurally disparate antibodies or epitope-binding fragments thereof that *have the same binding specificity as murine antibody EM164* and wherein said antibody *is substantially devoid of agonist*, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

It is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court's example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched "in terms of its function of lessening inflammation of tissues" which, the court stated, "fails to distinguish any steroid from others having the same activity or function". Similarly, the function of *having the same binding specificity as murine antibody EM164* and wherein said antibody *is substantially devoid of agonist* does not distinguish antibodies or epitope-binding fragments thereof, from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed

genus. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Finally to further address the reasons that antibodies comprising a heavy chain variable region with 90-95% identify to the heavy chain variable region of SEQ ID NO:7 or a light chain variable region with 90-95% identify to the light chain variable region of SEQ ID NO:8 are not adequately described, it is once again noted that the specification does not disclose any additions, deletions or mutations that could be made in the CDRs disclosed in these sequences nor does it disclose which CDRs could be removed in these sequences to obtain an antibody which would specifically bind IGF-IR and *have the same binding specificity as murine antibody EM164* and be *substantially devoid of agonist activity*. Once again, based on the art-recognized unpredictability that is present in making alterations in the CDR regions of a parent antibody, one of skill in the art could not immediately envision, recognize or identify which antibodies of these subgenera which would specifically bind IGF-IR and *have the same binding specificity as murine antibody EM164* and be *substantially devoid of agonist activity*.

Accordingly, after careful and complete consideration of Applicant's arguments, for these reasons, the specification as filed does not adequately describe the antibodies to which the claims are directed and this rejection is maintained.

15. The rejection of claims 2, 17, 30, and 32-34 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a NEW MATTER rejection.

At page 19 of the response filed March 18, 2008, Applicant has traversed this ground of rejection.

In this traversal Applicant appears to be arguing that the Office's position is contrary to 37 CFR 1.57 and that the facts in this case resemble the fact pattern in *Ex parte Maziere*.

In response, the Examiner respectfully disagrees because the agents in question do not appear in the large list of agents that appear in paragraph 93, as filed, and because applicant did not *particularly* point to disclosures in the DeVita et al. reference in paragraph 93 which particularly describe thalidomide, carmustine, pamidronate, prednisone, erythropoietin and bisohosphonate, *per se*.

Notably, at page 69, the specification contains the following incorporation by reference statement, "Certain patents and printed publications have been referred to in the present disclosure, the teachings of which are hereby each incorporated in their *respective entireties*[3] by reference".

Accordingly, while it appears that Applicant intended to incorporate the *entire* DeVita et al. reference, incorporating less than the entirety introduces new matter because it is clear that Applicant did not intend to only include the disclosure of DeVita et al. referencing thalidomide, carmustine, pamidronate, prednisone, erythropoietin and bisohosphonate, while *excluding* the rest of the disclosure of DeVita et al. For this reason, it is not contradictory to maintain that that the introduction of less than the entirety of DeVita et al constitutes new matter and this position in not contradictory to 37 CFR 1.57.

Secondly, while Applicant further points to the *Ex parte Maziere* conclusion of the Board, it is not apparent that the facts presented in the *Ex parte Maziere* conclusion are relevant to the instant case because in the *Ex parte Maziere* case dealt with an incorporation by reference statement of a US Patent Application to establish the priority of the claims in a continuation application, while the instant case incorporates non-patent literature, for example.

The Examiner respectfully submits that that the incorporation by reference standard required by 37 CFR 1.57 and at issue in the instant applicant is more

particularly addressed by the Federal Circuit in deciding *Advanced Display Systems Inc. v. Kent State University*, 54 USPQ2d 1673 (CA FC).

In this case, the Federal Circuit has opined[4]:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order have that material considered part of a later application); *cf. Lund*, 376 F.2d at 989, 153 USPQ at 631 (holding that a one sentence reference to an abandoned application is not sufficient to incorporate material from the abandoned application into a new application). Whether and to what extent material has been incorporated by reference into a host document is a question of law. *See Quaker City Gear Works, Inc. v. Skil Corp.*, 747 F.2d 1446, 1453-54, 223 USPQ 1161, 1166 (Fed. Cir. 1984) (reasoning that whether a document is incorporated by reference into a patent presents a question of law when determining enablement). *Id.* at 1679-1680.
>
> [Thus] the standard of one reasonably skilled in the art should be used to determine whether the host document describes the material to be incorporated by reference with sufficient particularity. *Id.* at 1680.

In this case, the mere reference at page 93 that Devita et al discloses therapeutic agents would not lead one of skill in the art to understand that Applicant intended to

[3] Emphasis added
[4] Underlining added

specifically only include the portions of Devita et al disclosing thalidomide, carmustine, pamidronate, prednisone, erythropoietin and bisohosphonate, while excluding all the other disclosure of Devita et al.

Thus, after a careful and full consideration of Applicant's arguments, the specification lacks information to lead one of skill in the art to understand that the applicant had possession of the broadly claimed invention at the time the instant application was filed. Therefore, one of skill in the art would not understand that the applicant had possession of the claimed invention at the time the instant application was filed and this rejection is maintained.

16. The rejection of claims 1-3, 6-19, 22, 24, 26, 27, 30-34 and 37 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a composition comprising an antibody or antigen-binding fragment thereof that specifically binds to an insulin-like growth factor-I receptor (IGF-I-R), wherein said antibody or antigen-binding fragment comprises a heavy chain variable domain comprising a CDR1 consisting of SEQ ID NO:1, a CDR2 consisting of SEQ ID NO:2, a CDR3 consisting of SEQ ID NO:3 and a light chain variable domain comprising a CDR1 consisting of SEQ ID NO:4, a CDR2 consisting of SEQ ID NO:5, a CDR3 consisting of SEQ ID NO:6, **and for making and using** antibodies encompassed by the claims and taught by the prior art, **does not reasonably provide enablement for making and using** a composition comprising (i) antibodies with the same binding specificity as murine antibody EM164 that are substantially devoid of agonist activity that do not comprise the amino acid sequence of the 6 CDRs of antibody EM164. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242

> U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Starting at page 21 of the amendment filed March 18, 2008, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

In the traversal, Applicant appears to be arguing that the claims are enabled, because "an antibody could be routinely made and used from a single CDR and that variation of an antibody wherein functional antibodies are obtained is routine in the art" citing the references of Holt et al, Aires da Silva et al, Tanaka et al and Peterson et al.

In response to this argument, as set forth in the above rejection of the claims as lacking adequate written description, the claims are still being interpreted as drawn to functional equivalents or variants of antibodies that have the same binding specificity as murine antibody EM164 and are substantially devoid of agonist activity, but do not require said antibody to comprise all 6 CDRs of the murine monoclonal antibody in their proper context of antibody framework regions, wherein the CDRs consist of SEQ ID Nos:1-6. For example, claim 1 does not require that the antibody comprise even a single CDR of the murine antibody EM164.

In further response, the Examiner respectfully disagrees that it was routine or conventional in the art to make antibodies comprising one CDR that are functionally equivalent to a parent antibody. While Applicant has identified art suggesting that for antibodies specific for some particular epitopes on some particular antigens, that functionally active peptides comprising less than all 6 CDRs of the murine monoclonal antibody in their proper context of antibody framework regions might be obtained, it has not been established that it is conventional or routine in the art to be able to make such peptides for any given parental antibody.

For example, as set forth in the above rejection of the claims as lacking adequate written description, Gussow et al (*supra*) teaches conventional methodologies for "humanizing" monoclonal antibodies which generally involve grafting the six CDRs from the light and heavy chain variable regions from a murine antibody into the framework of a human antibody. However, in general, if only one or two of the CDRs from either the light or heavy chain variable region were to be grafted, but not all three, the resultant antibody would not be expected to retain the binding affinity and specificity of the parent antibody.

As noted by Mariuzza et al. (*supra*), it is well established fact in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable domains of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced relatively early in the development of the art by Rudikoff et al. (*supra*). While Applicant has characterized the teachings of Rudikoff et al as an anomaly at page 22 of the response filed March 18, 2008, the Examiner respectfully disagrees because this sensitivity to such minor alterations has since been often observed a prevalent, if not frequent phenomenon[5].

[5] See, e.g., Winkler et al. (*J. Immunol.* 2000 Oct 15; **165** (8): 4505-4514), describing changing the specificity of an antibody by single point mutations (entire document; e.g., the abstract).

Thus, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*Proc. Natl. Acad. Sci. USA.* 1987 May; **84** (9): 2926-2930) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). Chien et al. (*Proc. Natl. Acad. Sci. USA.* 1989 Jul; **86** (14): 5532-5536) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions as a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*Mol. Immunol.* 2003 May; **39** (15): 941-952) (of record) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

Furthermore, it is apparent that it is not conventional or routine in the art to identify just one CDR that is essential for antigen binding or maintaining the conformation of the antigen binding site. For example, Casset et al. (*Biochem. Biophys. Res. Commun.* 2003 Jul 18; **307** (1): 198-205) describes the rational design and construction of a peptide mimetic of an anti-CD4 monoclonal antibody binding site; see entire document (e.g., the abstract). The peptide mimetic was designed with 27 residues formed by inclusion of residues from five of the six CDRs of the antibody; see, e.g., the abstract. Casset et al. states that although the heavy chain CDR3 is at the center of most, if not all antigen interactions, clearly other CDRs play an important role

in the recognition process (see, e.g., page 199, column 1). This conclusion is apparent given their demonstration that an active peptide mimetic that retains the ability to bind to the antigen necessarily comprises amino acids derived from all CDRs, except the light chain CDR2, in addition to a framework residue located just before CDR3 of the antibody's heavy chain; see, e.g., page 202, column 1. Though Casset et al. concedes that perhaps not all of the residues representing the various different CDRs will ultimately prove essential to the interaction, it will not be without further extensive studies that such a realization may be made (page 202, column 1).

The art of engineering functional recombinant antibodies, such as those to which the claims are directed, is even more confounded by findings that residues, which are positioned outside the recognized boundaries of the canonical CDRs, may contribute substantially to the interaction of an antibody and an antigen. For example, MacCallum et al. (*J. Mol. Biol.* 1996 Oct 11; **262** (5): 732-745) describes the discovery that although the residues of CDR3 of the heavy and light chains are dominant determinants of the interaction, a number of essential residues contacting the antigen have been placed outside the regions that are recognized using the conventional or standard definitions of the CDRs, which are generally used to define the components of the antigen binding site of the antibody; see entire document (e.g., page 733, column 2). Moreover, MacCallum et al. teaches an appreciation of the fact that residues within the CDRs that do not actually make contact with the antigen may be important because of their contributions to the conformation of the antibody's antigen recognition site; see, e.g., page 735, column 1.

Making further apparent the unpredictability of the importance of residues within the CDRs and other parts of an antibody, which must instead be determined empirically, Holm et al. (*Mol. Immunol.* 2007 Feb; **44** (6): 1075-1084) describes the mapping of residues important to the interaction of an anti-cytokeratin antibody with the antigen, where although residues in the CDR3 of the heavy chain were determined to be essential, they disclose their *unexpected* finding that a residue in CDR2 of the light chain forms a necessary part of the antigen binding site of the antibody contacting the

antigen; see entire document (e.g., the abstract). Thus, as recently as 2007, there are reports indicating despite the progress made toward understanding the interactions of antibodies and antigens, because of the unpredictable nature of the art, much information concerning the specificity and/or affinity of any given antibody cannot be gleaned by routine and conventional experimentation, but instead must be gathered by rigorous and undue experimentation.

Secondly, while Watkins et al (of record) teach an antibody comprising a light chain (Vk domain of HUI77) that is 95% identical to SEQ ID NO:8 and the antibody binds collagen, Applicant has argued that at no point do Watkins et al demonstrate that the antibody does not bind IGF-IR. However, by the same logic, Watkins et al presents no evidence that would lead one of skill in the art to conclude that this antibody would bind IGF-IR and as explained above, based on the state of the art in antibody-antigen recognition, it is highly unpredictable that the Watkins et al antibody binds IGF-IR. Accordingly, absent a showing otherwise, based on the disclosure of Watkins et al the antibody binds collagen which underscores the unpredictability in the art in making functionally equivalent antibodies in the art based on a recited percent amino acid identity alone.

Finally, Applicant has pointed to the Board's decision *Ex parte Kubin*, in which the board determined that claims directed to a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2 were found to be enabled even though the specification did not disclose any polypeptide variant of at least 80% identical to amino acids 22-221 of SEQ ID NO:2 with the same function as the polypeptide.

In response, Applicant is first reminded that each case is examined on its own merits and it is not apparent that the Board's decision *Ex parte Kubin* would fairly suggest that antibodies with the same binding specificity as murine antibody EM164 that are substantially devoid of agonist activity comprising a heavy chain variable region with 90% or 95% sequence identity to SEQ ID NO:7 or antibodies with the same binding specificity as murine antibody EM164 that are substantially devoid of agonist activity comprising a light chain variable region that has 90% or 95% sequence identity to SEQ

ID NO:8 are enabled, because as explained above, it is not routine in the art to make antibodies that comprise less than the 6 CDRs of a parent antibody which are functionally equivalent to the parent antibody. Accordingly, because the Examiner respectfully submits that the state of the art in the instant case indicates that undue and unreasonable experimentation would be required to make and use the instantly claimed antibodies this rejection is being maintained.

Once again, the specification has not provided any specific, non-general guidance as to how to make such functional equivalents or variants of antibodies that have the same binding specificity as murine antibody EM164 and are substantially devoid of agonist activity.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify other antibodies that are encompassed by the claims; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

In conclusion, upon careful and full consideration of Applicant's arguments and the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404

(Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation, and this rejection is being maintained.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. The rejection of claims 1, 6, 19, 22, 24 and 26 under 35 U.S.C. 102(b) as being anticipated by Zia et al (Journal of Cellular Biochemistry Supplement 24:269-275, 1996, IDS filed August 03, 2005), is maintained.

At page 25 of the amendment filed March 18, 2008, Applicant has traversed this ground of rejection.

In this traversal Applicant has argued that the insulin-like growth factor-I receptor antibody of Zia et al has significant agonist activity and therefore, Zia et al fails to anticipate the claims as amended which recite the antibody is substantially devoid of agonist activity.

In response, as set forth in the below rejection of the claims under 35 U.S.C. 112, second paragraph, it cannot be determined how substantially devoid of agonist activity the antibody must be or even which agonist activity the antibody must be substantially devoid of. The insulin-like growth factor-I receptor antibody of Zia et al would not have agonist activity for the majority of proteins it does not bind and therefore, it is broadly, but reasonably interpreted to be substantially devoid of agonist activity, absent a showing of any difference.

Accordingly, the products of Zia et al are materially and structurally indistinguishable from the instantly claimed products and the methods of Zia et al are materially and manipulatively indistinguishable from the instantly claimed methods.

For these reasons, the Examiner disagrees with Applicant's contention that Zia et al no longer anticipate the instant claims and the rejection of claims 1, 6, 19, 22, 24 and 26 under 35 U.S.C. 102(b), as being anticipated by Zia et al, is maintained.

19. The rejection of claims 1, 6, 19, 22, 24 and 26 under 35 U.S.C. 102(b) as being anticipated Rohlik et al (Biochemical and Biophysical Research Communications 149:276-281, November 30, 1987), is maintained.

At page 26 of the amendment filed April 16, 2007, Applicant has traversed this ground of rejection.

In this traversal Applicant has reiterated the argument that the amendment to the claims has obviated the rejection because Rohlik also disclose an insulin-like growth factor-I receptor antibody with substantial agonist activity.

In response, as set forth above, the insulin-like growth factor-I receptor antibody of Rohlik et al also would not have agonist activity for the majority of proteins it does not bind and therefore, it is broadly, but reasonably interpreted to be substantially devoid of agonist activity.

Accordingly, absent a showing of any difference, the products of Rohlik et al are materially and structurally indistinguishable from the instantly claimed products and the methods of Rohlik et al are materially and manipulatively indistinguishable from the instantly claimed methods.

For these reasons, the Examiner disagrees with Applicant's contention that Zia et al no longer anticipate the instant claims and the rejection of claims 1, 6, 19, 22, 24 and 26 under 35 U.S.C. 102(b), as being anticipated by Rohlik et al, is maintained.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

21. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

22. The rejection of claims 1-2, 24, 26-27, 30, 32 and 34[6] under 35 U.S.C. 103(a), as being unpatentable over Rohlik et al (Biochemical and Biophysical Research

[6] Claims 24, 30 and 34 were inadvertently omitted from this rejection previously. As set forth in the Office action mailed June 1, 1006, "Finally the claims are limited to a method of inhibiting the growth of cancer cells using the above composition." Furthermore, this Office action establishes that it would be obvious to "make a composition of the αIR-3 antibody of Rohlik and the PS-341 agent of Teicher and use it in research to inhibit the growth of MCF-7 cells as both were known to be useful for the same purpose, i.e. inhibiting the growth of MCF-7 cells, so it would be *prima facie* obvious to combine two products that are useful for the same purpose to form a composition which is to be used for the very same purpose". Furthermore, since they are useful for the same purpose it would be obvious to contact the cell

Communications 149:276-281, November 30, 1987), in view of Teicher et al (Clinical Cancer Research 5:2638-2645, September 1999), is maintained.

At page 27 of the amendment filed March 18, 2008, Applicant has traversed this ground of rejection.

In this traversal, Applicant has reiterated that the antibody of Zia et al has significant agonist activity and for this reason the instant claims are not obvious.

In response, as explained above, the Examiner disagrees that the antibody of Zia et al would not be considered to be substantially devoid of agonist activity.

Furthermore, as set forth in the preceding Office action it would be obvious to combine the antibody of Rohlik with the bortezomib of Teicher et al as both agents are useful for the same purpose.

For these reasons, the Examiner disagrees with Applicant's contention that the rejection should be withdrawn and the rejection of claims 1-2, 24, 26-27, 30, 32 and 34 as being unpatentable over Rohlik et al in view of Teicher et al is maintained.

23. The rejection of claims 1 and 37 under 35 U.S.C. 103(a) as being unpatentable over Zia et al (Journal of Cellular Biochemistry Supplement 24:269-275, 1996, IDS filed August 03, 2005), in view of Queen et al (U.S. Patent 5,530,101, 6/25/1996, IDS filed August 03, 2005), is maintained.

At page 28 of the amendment filed March 18, 2008, Applicant has traversed this ground of rejection.

In this traversal, Applicant has reiterated that the antibody of Zia et al has significant agonist activity and for this reason the instant claims are not obvious.

In response, as explained above, the Examiner disagrees that the antibody of Zia et al would not be considered to be substantially devoid of agonist activity.

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concurrently or sequentially in either order to access whether any differences in cell-killing results from the order of contact. For these reasons, these claims have been added to this rejection. The Examiner apologizes for any inconvenience to Applicant or Applicant's representative that this issue may raise.

Furthermore, as set forth in the preceding Office action it would be obvious to humanize the antibody of Zia et al in view of Queen et al because the murine monoclonal antibody IR-3 inhibits growth of human lung cancer cells.

For these reasons, the Examiner disagrees with Applicant's contention that the rejection should be withdrawn and the rejection of claims 1 and 37 as being unpatentable over Zia et al in view of Queen et al is maintained.

24. The rejection of claims 1 and 37 under 35 U.S.C. 103(a) as being unpatentable over Rohlik et al (Biochemical and Biophysical Research Communications 149:276-281, November 30, 1987), in view of Queen et al (U.S. Patent 5,530,101, 6/25/1996, IDS filed August 03, 2005), is maintained.

At page 28 of the amendment filed March 18, 2008, Applicant has traversed this ground of rejection.

In this traversal, Applicant has reiterated that the antibody of Rohlik et al has significant agonist activity and for this reason the instant claims are not obvious.

In response, as explained above, the Examiner disagrees that the antibody of Rohlik et al would not be considered to be substantially devoid of agonist activity.

Furthermore, as set forth in the preceding Office action it would be obvious to humanize the antibody of Rohlik et al in view of Queen et al because the murine monoclonal antibody, alpha IR-3 inhibits growth of human breast cancer cells.

For these reasons, the Examiner disagrees with Applicant's contention that the rejection should be withdrawn and the rejection of claims 1 and 37 as being unpatentable over Rohlik et al in view of Queen et al is maintained.

Double Patenting

25. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims

are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

26. The provisional rejection of claims 1-3, 6-18, 32-33 and 37 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of copending Application No. 10/170,390 in view of Teicher et al, is maintained for the reasons of record, as explained in the previous Office action.

At page 27 of the amendment filed March 18, 2008, Applicant has noted that both Applications are currently pending and requested that the rejection be held in abeyance.

In response, the rejection will be maintained until it is appropriately resolved.

27. The provisional rejection of claims 19, 22, 24, 26, 27, 30, 31 and 34 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claim 30 of copending Application No. 10/170,390 in view of Teicher et al, is maintained for the reasons of record, as explained in the previous Office action.

At page 27 of the amendment filed March 18, 2008, Applicant has noted that both Applications are currently pending and requested that the rejection be held in abeyance.

In response, the rejection will be maintained until it is appropriately resolved.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

28. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

29. Claims 1-3, 6-19, 22, 24, 26, 27, 30-34 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 6-19, 22, 24, 26, 27, 30-34 and 37 are indefinite for reciting the phrase "substantially devoid of agonist activity" in claim 1. In this case, the term "substantially" is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In this case, it is not apparent to what requisite degree or under what conditions the antibody must be "substantially devoid of agonist activity" to be regarded as "substantially devoid of agonist activity". Furthermore, because claim 1 only recites "agonist activity" without identifying any agonist activity, this recitation renders the claim indefinite because many activities can be agonized and it is unclear to which activity the claim is directed. Which of the expected plurality of agonist activities must the antibody be substantially devoid of? The claims cannot be construed unambiguously without knowing the answer to this question. For these reasons, the claims fail to delineate the subject matter that Applicant regards as the invention with the requisite degree of clarity and particularity to permit the skilled artisan to know or determine infringing and non-infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim Rejections - 35 USC § 103

30. Claims 1-3, 24, 26-27 and 30-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zia et al (Journal of Cellular Biochemistry Supplement 24:269-275, 1996, IDS filed August 03, 2005), in view of Lam et al (HKMJ, 5(2):180-186, 1999).

The claims are herein interpreted as being drawn to a composition comprising an antibody that is the functional equivalent of monoclonal antibody EM164 that specifically binds to insulin-like growth factor-I receptor and a second agent, wherein the second agent is gemcitabine. Finally the claims are limited to a method of inhibiting the growth of cancer cells using the above antibody and gemcitabine by contacting the cell with said antibody and said gemcitabine concurrently or sequentially in either order.

Zia et al teach the antibody, IR-3 that specifically binds to insulin-like growth factor-I receptor (see whole document, e.g., page 270) and is being considered a functional equivalent of murine antibody EM164 since it has the same binding specificity as EM164 and, as explained above, appears substantially devoid of agonist activity. (see entire document, e.g., page 276, first paragraph). Finally, Zia et al teach αIR-3 conjugated to ^{125}I and that this composition inhibits the growth of human lung cancer cells (e.g., page 273). Zia et al do not expressly teach said αIR-3 antibody in a composition with gemcitabine. This deficiency is made up for in the teachings of Lam et al.

Lam et al teach that gemcitabine is a cytotoxic agent to human lung cancer cells (see entire document, e.g., abstract and page 183).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was make to make a composition of αIR-3 conjugated to ^{125}I and gemcitabine and use it in basic research to inhibit the growth of human lung cancer cells. Furthermore, since these agents are useful for the same purpose, it would be obvious to contact the cell concurrently or sequentially in either order to access whether any differences in cell-killing results from the order of contact.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention to make a composition of the of αIR-3 antibody conjugated to ^{125}I of Zia and gemcitabine of Lam and use it in research to inhibit the growth of human lung cancer cells as both were known to be useful for the same purpose, i.e. inhibiting the growth of human lung cancer cells, so it would be *prima facie* obvious to combine two products that are useful for the same purpose to form a composition which is to be used for the very same purpose. See In re Kerhoven, 626 F.2d 848, 850, 205 USPQ 1069, 1072, (CCPA 1980). Thus, there would be an advantage and a reasonable expectation of success in making a composition of αIR-3 conjugated to ^{125}I and gemcitabine and use it in research to inhibit the growth of human lung cancer cells, in view of Zia et al and Lam et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

31. No claim is allowed.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
June 9, 2008